

BXTD 9005
ELX-5704 (US)
PATENT

D¹
For example, under the conditions of an exhypoxic polycythemic mice assay (see, *Nature* (1961) 191:1069-1087), values ranging from about 40,000 to about 65,000 U/mg are observed for Epoetin Omega. Radioimmunoassay results indicate an *in vitro* biological activity in the range of about 200,000 to about 240,000 U/mg for Epoetin Omega. Purified urinary EPO has been reported to have an *in vivo* activity from about 45,000 IU upwards to about 75,000 or more per mg. In addition, there are likely corresponding differences in the secondary or tertiary structures of the recombinant Erythropoietins (i.e., protein structure/folding) as well as the established differences in carbohydrate composition and bonding strength thereof, as well as stability of the various glycoproteins even though the primary protein sequence may be identical. Each known form of recombinant erythropoietin is a glycoprotein having a myriad of complex carbohydrate chains that include sugars that are N-linked to amino residues and/or O-linked to hydroxy residues. However, the content amount, number, position, bond strength, structure and composition of the carbohydrate linkages differ between the different recombinant erythropoietins and between urinary human erythropoietin. The structure and composition of Epoetin Omega carbohydrate residues has been described for example, by Nimtz et al. *Eur. J. Biochem.* 213:39, (1993); Tsuda et al. *Eur. J. Biochem.* 188:405, (1990); and Sytkowski et al., *Biochem. Biophys. Res. Comm.* 176:698, (1988) each of which are incorporated herein by reference in their entirety.

Please replace the paragraph beginning at page 47, line 3 with the following rewritten paragraph:

D²
Epoetin Omega is typically formulated in doses of 2000 or 4000 IU/ml with a pharmaceutically acceptable carrier or diluent for subcutaneous (s.c) or intravenous (i.v) injection. An example carrier or diluent in a 1 ml volume might include: sodium chloride (NaCl) 8.18 mg, monobasic sodium phosphate ($\text{NaH}_2\text{PO}_4 \cdot \text{xH}_2\text{O}$)

BXTD 9005
ELX-5704(US)
PATENT

D² 1.56 mg, sodium hydroxide (NaOH) to pH 7.2, and human serum
albumin 1.0 mg.
